Specialty Conference

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Complications of Oral Contraceptive Agents

—A Symposium

Action and Efficacy of Systemic Contraceptive Agents, and Introduction of Complications

RONALD S. SWERDLOFF, MD*

THE NEED FOR population control has been emphasized repeatedly by numerous social and biological scientists over the past few decades. The almost geometrical population growth in the world is shown in Chart 1. This chart, prepared only a few years ago, allowed for the projected further expansion (dashed line) if the population is not further controlled.[1] The gravity of the situation can be seen from the following calculations. In 1969 the world population stood at 3.6 billion people. It was estimated then that in the next 31 years the world population would more than double and by the year 2040 would reach 14 billion, or a quadrupling of the population in 70 years.[2]

This projected growth has raised great concern. Two important questions have been raised: (1) Will there be adequate foodstuff to maintain life (of whatever quality), and (2) what happens to people when they are overcrowded even if nutrition is adequately maintained? The effect of the world population expansion on food supplies has been recently emphasized to us by the 1973 world food shortage and the resultant inflated food prices. Recently reported long-term studies on overcrowding of mice housed in a predator-free, germ-free, controlled environment with ample food may well predict the potential risk to man. In these studies, after a sharp population expansion, social behavior deteriorated badly and ultimately stopped and the colony became extinct two and a half years later.

With the problem thus defined, we can look at the present state of the art of birth control. While there are many ways of limiting reproduction—such as sexual abstinence (rhythm method), physical obstruction to fertilization (condoms and diaphragms), interference with implantation by local means (intrauterine device)—this symposium will

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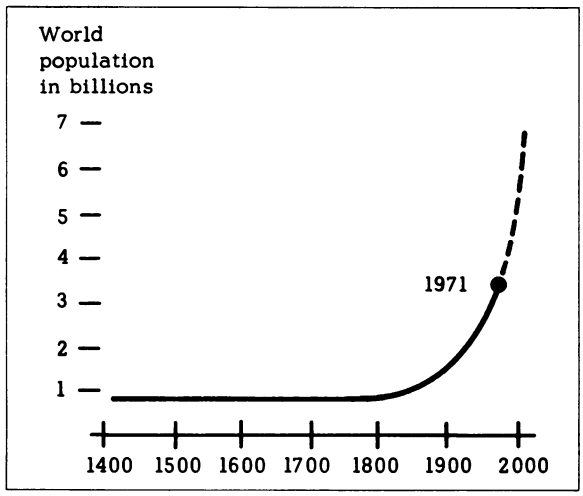

Chart 1.—Long term changes in world population. The dashed line represents the projected population as of 1971. (Reproduced by permission from Odell WD: Reproductive biology, **In** Odell WD, Moyer DL: Physiology of Reproduction. St. Louis, Mo., The C. V. Mosby Company, 1971)

limit itself to a discussion of systemic contraceptives, their mechanisms of action, and their effectiveness and side effects.

Hormonal Control of Ovulation

The hormonal events responsible for ovulation are complex and only recently becoming fully understood. Chart 2 represents the changes in serum levels of two pituitary hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), and three gonadal steroids, estradiol (E_2), progesterone (P), and 17α hydroxyprogesterone (17P) during a normal menstrual cycle.

FSH rises early in the cycle. This rise in the presence of permissive concentrations of serum LH stimulates ovarian follicular growth and maturation which in turn results in increasing secretion of estradiol and 17α hydroxyprogesterone. When estradiol reaches a critical level, it acts on the hypothalamic-pituitary axis to stimulate the release of a large amount of LH and, to a lesser extent, FSH. These gonadotropins induce the mature follicle to release its ovum and a corpus luteum is formed. Progesterone, now secreted in increasing amounts, and estrogen, which has remained high, act to inhibit the secretion of LH and FSH and prepare the uterus for the potential implantation of a fertilized egg. In time, the ovarian secretion of estradiol and progesterone diminishes and in the absence of pregnancy, uterine mucosal sloughing occurs resulting in menses. The fall in estrogen and progesterone then acts to stimulate the hypothalamic-pituitary axis to secrete FSH and a new cycle is begun. The interruption of this cycle is one of the important mechanisms by which many of the steroid contraceptive agents work.

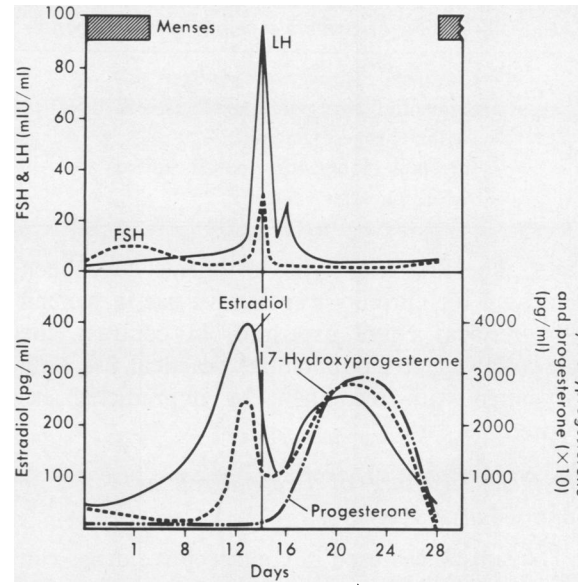

Chart 2.—Schematic representation of the fluctuations in serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone, 17-hydroxy-progesterone, and estradiol during the normal menstrual cycle in women. Note that both estradiol and 17-hydroxy-progesterone rise before the LH-FSH ovulation surge. In order to show progesterone and 17-hydroxyprogesterone on the same scale, progesterone concentrations were divided by 10; that is, they are actually ten times greater than shown. (pg/ml=picograms per milliliter) (Reproduced by permission from Odell WD, Moyer DL: Physiology of Reproduction. St. Louis, Missouri, The C. V. Mosby Company, 1971)

Following ovulation the ovum is transported down the fallopian tube where it is fertilized by a sperm. The sperm responsible for fertilization is one of millions deposited into the vagina; the deposited sperm migrates through the cervical mucus into the uterus and ultimately into the fallopian tube. The fertilized ovum continues to move down the fallopian tube and into the uterus which has been prepared for implantation by the proper balance of ovarian steroids. Alterations of cervical mucus, impaired or accelerated tubal transport of the ovum, or lack of proper uterine preparedness for implantation are all factors by which systemic agents could have important contraceptive effects.

Systemic Contraceptive Agents

Table 1 lists the five types of systemic contraceptive agents which have received adequate clinical trials and are available for use in the United

TABLE 1.—*Types of Systemic Contraceptive Agents*

- Combined estrogen-progestogen pill
- Sequential estrogen-progestogen pill
- "Mini" progestogen pill
- Injectable long-acting contraceptive
- "Morning after" pill

States. The first four types of agents have been advocated for chronic preventative use in women with frequent coital exposure. In contrast, the post-coital agent has potential practical use only in women with infrequent or unpredicted exposure.

Chemical Structure of Drugs Used as Contraceptive Agents

The substances used in contraceptive drugs can be generally divided into estrogenic and progestational agents. The estrogens are usually synthetic steroid substances (Chart 3B) but in the case of the post-coital pill may be of a non-steroidal variety such as stilbestrol. The progestational agents are either 19-nortestosterone derivatives (Chart 3C) or are 17 acetoxy-progesterone derivatives (Chart 3D). These estrogenic and progestational agents are representatives of the compounds that are used either alone or in a combination in the various types of contraceptive drugs. Their metabolic effects are obviously different and their pathogenic role in the specific side-effects seen with contraceptives differ.

Combined Estrogen Plus Progestogen Agents

Combined estrogen and progestogen agents have been used clinically for almost 20 years. They consist of an estrogen combined with a progestogen in various combinations (Table 2).[3] The single pill is given daily from the fourth day after onset of menses to day 24 of the cycle, is discontinued to allow withdrawal bleeding, and then is reinstated.

The mechanism of action of these agents can be seen in Chart 4. With the use of continued agents, the complex hormonal changes seen in Chart 2 are blocked. The early FSH rise does not occur, a mid-cycle LH surge is absent, and ovulation is prevented.[4] Evidence that the inhibition may occur at the hypothalamic level includes the demonstration that an LH surge can be produced in female rats administered contraceptive preparations following the injection of the hypothalamic releasing hormone, LRH.[5]

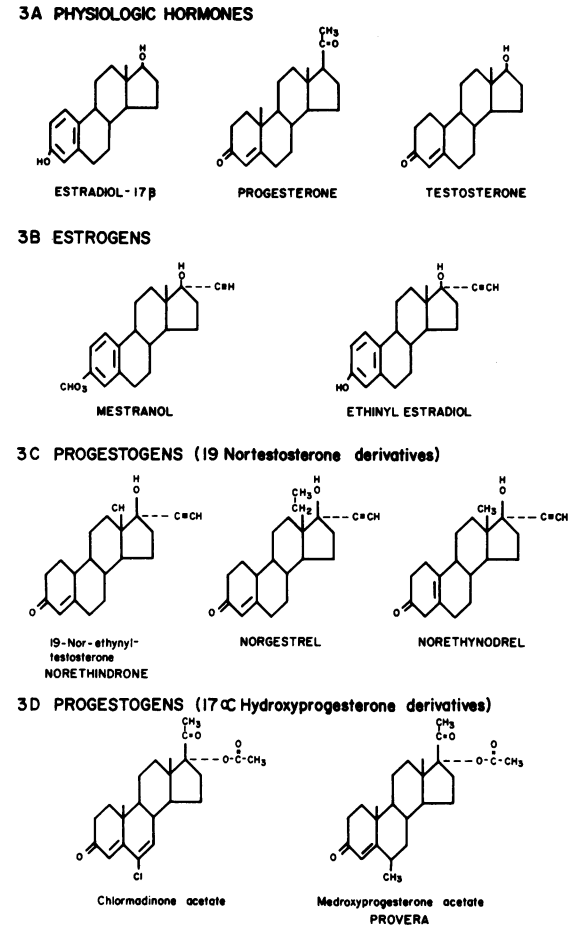

Chart 3.—Chemical structure of drugs used as contraceptive agents. Contraceptive agents may include one or more steroid substances.

The effectiveness of combined contraceptives when taken faithfully has been remarkable, resulting in a pregnancy rate of only 1 per 1,000 women years.[3]

Sequential Contraceptives

Sequential contraceptives, also containing estrogen and progestogen agents, differ from the combined contraceptives in that the estrogen medication is given alone for the first 15 to 20 days of the cycle, then is followed by combined estrogen and progestogen treatment for a short time.

The estrogen component of these drugs (see Table 1) also inhibits ovulation, but results in a different pattern of serum LH and FSH than that seen with the combined drugs[4] (Chart 5). In this study, ethinyl estradiol given alone inhibited FSH but resulted in multiple spikes of LH. It has been presumed that the follicle did not mature properly and therefore was not responsive to the LH surges which might occur close to the usual time.

TABLE 2.—*Various Combinations of Progestogen and Estrogen in Commercially Available Contraceptive Agents**

COMBINATION	*Progestogen : Estrogen*	*Trade Names (Manufacturers)*	*Administration*
Ethynodiol diacetate ...	1 mg : 100 μg mestranol	Ovulen (Searle)	From 5th through 24th or 25th day of cycle or 21 days of treatment followed by 7 days during which no pills are taken or iron containing 75 mg ferrous fumarate tablets are taken. The number 20 or 28 following the trade name indicates number of tablets in package.
	1 mg : 50 μg ethinyl estradiol	Demulen (Searle)	
Norethindrone	10 mg : 60 μg mestranol	Norinyl 10 mg (Syntex) Ortho-Novum 10 mg (Ortho)	
	2 mg : 100 μg mestranol	Norinyl 2 mg (Syntex) Ortho-Novum 2 mg (Ortho)	
	1 mg : 80 μg mestranol	Norinyl+80 (Syntex) Ortho-Novum 1/80 (Ortho)	
	1 mg : 50 μg mestranol	Norinyl+50 (Syntex) Ortho-Novum 1/50 (Ortho)	
Norethindrone acetate ..	2.5 mg : 50 μg ethinyl estradiol	Norlestrin 2.5 mg (Parke, Davis)	
	1 mg : 50 μg ethinyl estradiol	Norlestrin 1 mg (Parke, Davis)	
Norethynodrel	9.85 mg : 150 μg mestranol	Enovid 10 mg (Searle)	
	5 mg : 75 μg mestranol	Enovid 5 mg (Searle)	
	2.5 mg : 100 μg mestranol	Enovid-E (Searle)	
Norgestrel	0.5 mg : 50 μg ethinyl estradiol	Ovral (Wyeth)	
SEQUENTIAL			
Dimethisterone	25 mg : 100 μg ethinyl estradiol	Oracon (Mead Johnson)	Ethinyl estradiol for 16 days, then dimethisterone plus ethinyl estradiol for 5 days.
Norethindrone	2 mg : 80 μg mestranol	Norquen (Syntex)	Mestranol for 14 days, then norethindrone plus mestranol for 6 days.

*Adapted from JAMA 214:2318, Dec 28, 1970.

In addition, a direct effect of estrogen and progestogen drugs on the endometrium results in impaired implantation of a fertilized ovum and provides protection above and beyond their anti-ovulatory role.

While the sequential drugs were attractive initially because of the attempt to simulate a normal hormonal milieu more closely, they have proved to be less effective than the combined drugs, allowing a pregnancy rate of approximately 5 per 1,000 women years, a five-fold increase over the combined drugs under omission-free conditions.

The Mini Pill

In the early 1960's, studies began on the possibility of using progestational compounds in smaller and smaller doses (without the addition of estrogen compounds) as a means of conception control. As the controversies over estrogen and thromboembolism grew, the potential attractiveness of this approach increased.

A number of 19-nortestosterone and 17 acetoxy-progesterone derivations used in microgram doses have been referred to as "mini pills." They are administered once daily in a continuous fashion. Theoretically, menstrual bleeding occurs on a regular basis simulating normal menses.

The pregnancy rate from these compounds varies from 0 to 16.4 pregnancies per 1,000 women years (Table 3),[6] depending on which series is examined. The average pregnancy rate appears to be about 3 per 1,000 women years, a figure which is acceptable, but significantly higher than that for the combined contraceptives.

The mechanisms of action of these compounds are complex, but inhibition of sperm penetration through cervical mucus seems to be one of the most important.[2,7,8] Ovulation suppression appears to be an inconsistent action of the microdoses of these drugs,[6,9,10] and irregular multiple and non-predictable LH peaks may be seen in women taking them.[10,11]

Other described effects of these drugs include impaired function of the corpus luteal secretion of steroids, possible altered tubal transport and impaired uterine receptiveness to implantation. The major clinical problems other than the increased pregnancy rate from these compounds is the high

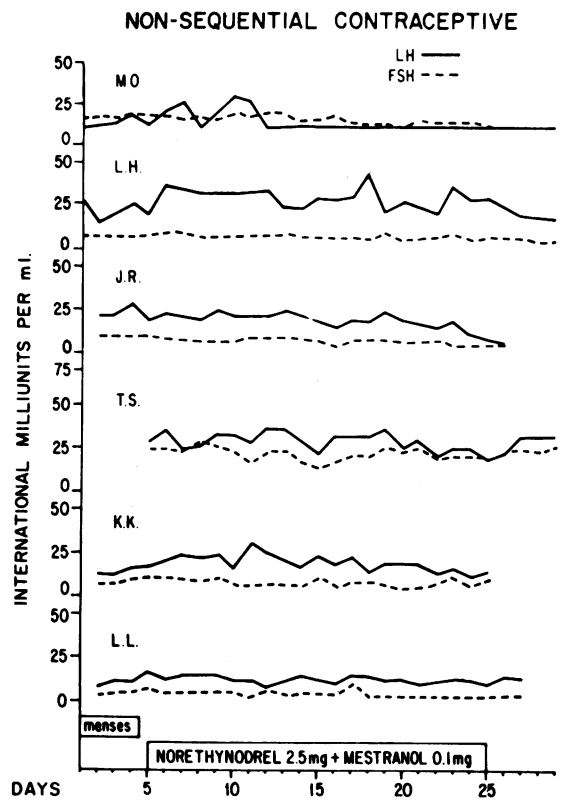

Chart 4.—Serum LH and FSH concentration measured daily in 6 eugonadal women receiving the combination of norethynodrel, 2.5 mg, and mestranol, 0.1 mg, from day 5 to day 25 of the menstrual cycle. (Reproduced by permission from Swerdloff RS, Odell WD: J Clin Endocrinol 29:157, 1969)

frequency of intermenstrual bleeding and prolonged amenorrhea while taking them.

Long-Acting Hormonal Contraceptives

Long-acting systemic contraceptive agents have been evaluated in both an oral and an intramuscular form. The parenteral preparations have received the greatest consideration. These have consisted of two types: (1) a high dose of the depo form of progestogen—for example, depo-medroxyprogesterone acetate (DMPA)—and (2) combined depo progestogen and estrogen.

DMPA has been investigated most. The effectiveness of this drug has been demonstrated by Mishell,[12] who found no pregnancies in 5,399 patient months of experience on a regimen of 150 mg of DMPA intramuscularly every three months. Two problems occur with this regimen. Irregular vaginal bleeding occurs frequently during the first six months of therapy. This bleeding decreases with time and amenorrhea is usually seen by one year.

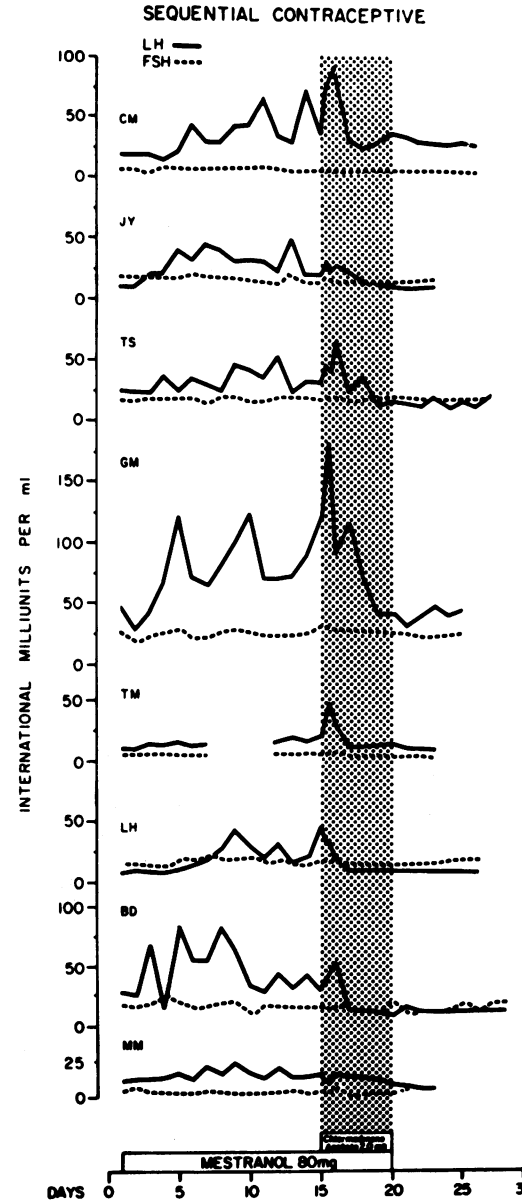

Chart 5.—Daily serum LH and FSH concentrations in eight women receiving a sequential type contraceptive. (Reproduced by permission from Swerdloff RS, Odell WD: J Clin Endocrinol 29:157, 1969)

Amenorrhea may persist after discontinuation of the drugs. Scutchfield et al[13] found 23 percent of patients had amenorrhea at 12 months post-treatment while Gardner and Mishell[14] found that nearly all had resumed menses, become pregnant or had a secretory endometrium by 18 months post-therapy.

The mechanism of action of DMPA may include effects on sperm penetration and uterine receptiveness, but inhibition of ovulation appears to be regularly observed. Cyclic LH and FSH discharge is

TABLE 3.—*Pregnancy Rate from Low-Dose Progestogens**

Investigator	*Drug*	*Dose (mg)*	*Number of Cycles*	*Pregnancy Rate in 100 Woman Years*
Martinez-Manautou et al (1967)	Chlormadinone acetate	0.5	25,158	3.6
Butler and Hill (1969)	Chlormadinone acetate	0.5	1,642	9.5
Espagno (1969)	Chlormadinone acetate	0.5	710	9.5
Jeppson and Kullander (1969)	Chlormadinone acetate	0.5	2,021	1.8
Howard et al (1969)	Chlormadinone acetate	0.5	2,080	8.6
Larsson-Cohn (1970)	Chlormadinone acetate	0.5	1,909	3.2
Bernstein and Seward (1972)	Chlormadinone acetate	0.5	3,199	4.5
Foss et al (1968)	Norgestrel	0.05	2,250	3.2
Satterthwaite et al (1969)	Megestrol acetate	0.50	1,319	16.4
Larsson-Cohn (1970)	Norethindrone	0.50	1,600	0.8
Larsson-Cohn (1970)	Norethindrone	0.40	1,299	0
Larsson-Cohn (1970)	Norethindrone	0.30	2,395	1.5
Rubio et al (1972)	Quingesterol	0.30	2,489	1.9

*Reprinted by permission from Larsson-Cohn U: Acta Endocrinologica 64:Supplement No. 144, 1970.

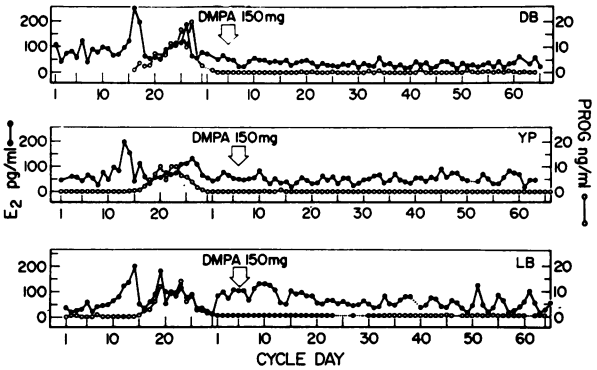

Chart 6.—Daily serum estradiol and progesterone levels in three women for one control cycle and two months after receiving an injection of 150 mg of DMPA (arrow). (Reproduced by permission from Mishell DR Jr, Kharma KM, Thorneycroft IH, et al: Am J Obstet Gynecol 113: 372, 1972)

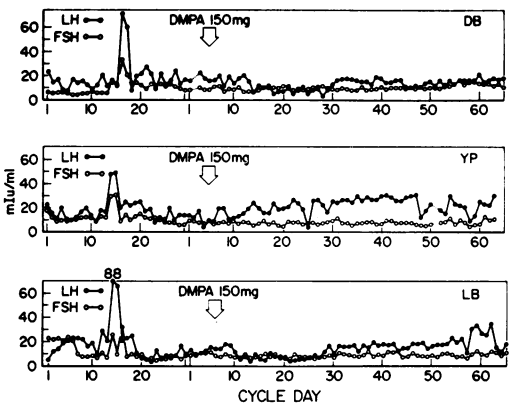

Chart 7.—Daily serum LH and FSH levels in the same three women as Chart 6. (Reproduced by permission from Mishell DR Jr, Kharma KM, Thorneycroft IH, et al: Am J Obstet Gynecol 113:372, 1972)

inhibited and estradiol levels remain in the early follicular range (Charts 6 and 7).

Another approach for depo progestogens has been the use of silastic and silicone rubber implants of the progestogen megestrol acetate. The pregnancy rate in a study by Coutinho et al[15] was estimated to be between 1 and 3 per 1,000 women years, depending on their analysis.

Injectable depo progestogen combined with either estradiol enanthate or depo estradiol cypionate has received some trials but appears to have little advantage over DMPA alone.[16,17]

In summary, the long-acting depo preparations, none of which have been released by the Federal Drug Administration for use as contraceptives, would appear to be effective means of preventing childbirth. They suffer from the disadvantages of irregular bleeding and the reservations about persistent post-treatment amenorrhea which occurs in some patients. If they are ever released for general use, they would appear to have the greatest possible role in patients who for various reasons are unreliable pill takers.

The "Morning After" Pill

Post-coital contraception has received considerable attention in both the lay and the scientific press. Both estrogens (diethyl stilbestrol) and progestogens (norethindrone) have been considered for this purpose. One synthetic estrogen, diethyl stilbestrol (DES) has received clinical trial. Twenty-five milligrams twice daily for five days begun within 72 hours of sexual exposure resulted in no pregnancies in 1,000 women of childbearing age.[18] The side-effects consisted mainly of nausea and vomiting, in about 13 percent of the patients. The mechanism of action is thought to be disturbance to tubal transport of the ovum, resulting in

TABLE 4.—*Some of the Side-Effects, Real or Purported, Ascribed to Estrogen-containing Contraceptive Agents*

Minor
Weight gain and edema
Nausea, vomiting and change in bowel habits
Vaginal spotting
Migraine headaches
Increased serum globulins-confusion in hormone measurement
Chloasma
Hirsutism
More Serious
Hypertension
Thrombophlebitis and embolic disease
Intrinsic vascular changes
Cerebral vascular occlusive disease
Impaired carbohydrate tolerance
Unknown risk of cervical neoplasia
Liver disease
Hyperlipidemia
Post treatment amenorrhea and galactorrhea

the premature presence of the ovum in an unprepared uterus.[19] This form of contraception has little attractiveness for use in women with frequent coital exposure. It does have great potential, however, for the women with infrequent or unpredicted exposure, including cases of criminal rape.

One progestogen, norethindrone, in large doses was found to provide low protection as a postcoital contraceptive.[20]

Complications of Contraceptives

Whenever drugs are administered to healthy persons for experimental or prophylactic purposes, great concern is appropriately expressed about possible side-effects. When such drugs are administered to millions of people, even a low incidence of serious side-effects may become an important health problem; such is the case with the estrogen-containing contraceptives. These agents, initially demonstrated in animal or human trials to be remarkably safe, now, after almost two decades of use by patients, have been demonstrated to have many minor and a few, although unusual, serious side-effects.[21] Many of these real or purported side-effects are listed in Table 4.

The minor complications of vaginal spotting, edema, nausea, and chloasma are not uncommon. Migraine headaches can be a troubling problem in predisposed women. The migraine seems to be precipitated by the falling levels of steroids which occurs at the time of monthly discontinuation of therapy.

Estrogens have many metabolic effects on the liver. These effects will be discussed in detail later by Dr. Fisher.

Also seen in Table 4 are the more serious side-effects. An analysis of the role of contraceptive agents in the production of these complications will be presented in the following sections.

An Analysis of the Reported Association of Oral Contraceptives to Thromboembolic Disease

WILLIAM D. ODELL, MD, PhD*

DR. SWERDLOFF has reviewed the mechanism of action and various types of oral contraceptives in present use. Oral contraceptives have become one of the commonest forms of contraceptive devices and millions of women throughout the world have been taking them for several months to many years. While the incidence of serious side-effects attributed to these drugs is low, some of them are life-threatening. If these side-effects are causally related to oral contraceptive treatment, then the total number of people affected will be very large. Thus, understanding the cause-and-effect relationship of side-effects should be thorough. At the outset it should be said that the possible statistical increase in life-threatening side-effects in women without predisposing factors is very low. We will attempt to put that in perspective later in this review.

Thromboembolic Disease

The initial studies in the United States reported that women receiving oral contraceptives were no more likely to have thrombophlebitis or embolic phenomena than were those not receiving oral contraceptives. For example, in 1963 the Food and Drug Administration of the United States reviewed more than 350 reports of thromboembolic diseases in women taking Enovid® (norethynodrel with mestranol).[22] They estimated that among white women taking Enovid the mortality from thromboembolic disease was 12.1 per million, whereas the comparable mortality in the general

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